ULTRASONIC IMAGING OF PERFUSION AND BLOOD FLOW
WITH HARMONIC CONTRAST AGENTS

This invention relates to ultrasonic diagnostic
imaging systems and, in particular, to the use of
ultrasonic imaging to segment and visualize perfusion
of tissue and blood vessel flow with ultrasonic
contrast agents.

Ultrasonic diagnostic imaging has benefited from
the enhancement of perfusion studies and blood flow
imaging with harmonic contrast agents for a number of
years. In a typical study the contrast agent is
introduced into the patient intravenously.
Ultrasonic imaging is then commenced at a region of
interest such as the heart or blood vessels. As the
injected bolus of contrast agent begins arriving at
the region of interest the microbubbles of the
contrast agent return relatively strong ultrasonic
echoes. Furthermore, these echo signals have
significant nonlinear (*e.g.,* second harmonic)
components. Detecting signals at the second harmonic
of the transmit frequency thus produces signals from
the contrast agent which dominate those returned by
other reflectors in the body. An image which maps
the locations of the contrast agent in the body thus
reveals the locations of the blood flow which carries
the microbubbles, and images produced from the second
harmonic signals and other harmonic components
segment out the locations of blood flow to the
relative exclusion of the surrounding tissue.

The use of contrast agents to image the
perfusion of microvasculature in tissues such as the
myocardium or liver has been found to produce
excellent results which enable various techniques for
quantifying the perfusion of tissue with a flow of

blood. As used herein, the term "perfusion" relates
to the amount of blood flow per volume of tissue.
With the advent of low power (low MI) contrast agents
and techniques, a single dose of contrast agent can

5   provide a relatively long period during which the
contrast agent is present in the body and perfusing
the tissue. However, such long imaging periods are
generally not prevalent when imaging and diagnosing
larger blood vessels. The larger arterial blood

10   vessels will usually begin to fill first following
the bolus injection of the contrast agent and can
initially be imaged with good results. But in time
the contrast agent will begin to fill the
microvasculature of the surrounding tissue, obscuring

15   the flow of contrast agents in the larger vessels.
One technique for dealing with this problem is to
image at a higher MI which is just high enough to
continuously destroy the slower moving microbubbles
in the microvasculature of the region of interest

20   while continuing to visualize the faster moving
microbubbles in the larger vessels. This approach
will reduce the effective imaging time because the
contrast agent is constantly being destroyed.
Furthermore, it is often difficult to adjust and

25   maintain the appropriate transmit power levels in a
clinical environment to maintain the constant
destruction of microvasculature microbubbles without
significantly disrupting those in the larger vessels.
It would be desirable to be able to image both

30   contrast agent tissue perfusion and the flow of
contrast agents in the larger vessels simultaneously
as both provide significant useful clinical
information. But it is desirable to do so in a way
which affords substantial contrast agent imaging time

to enable the most comprehensive and accurate
diagnosis of the patient.

In accordance with the principles of the present
invention, an ultrasonic diagnostic imaging system
5   and method are described which provide the
simultaneous imaging of both tissue perfusion and
larger vessel blood flow by contrast agents.
Multiple, differently modulated transmit signals are
used to acquire ensembles of echo information from
10   points within a region of interest. The ensembles
are differently filtered to produce contrast agent
signals characteristic of perfusion and/or higher
velocity blood flow. The ultrasound system uses
these signals to produce an image of the blood flow
15   in larger vessels against a background of tissue
perfusion. The clinician is thus able to visualize
tissue perfusion and larger vessel flow
simultaneously with the larger vessel flow clearly
segmented against the perfusion background.
20   In the drawings:
FIGURE 1 illustrates in block diagram form an
ultrasound system constructed in accordance with the
principles of the present invention.
FIGURE 2 is a detailed block diagram of the
25   contrast signal filtering of the detection and
classification of ultrasound signals from different
sources in the ultrasound system of FIGURE 1.
FIGURES 3a-3c illustrate the characteristics of
the filters of FIGURE 2.
30   FIGURE 4a-4b illustrate response characteristics
useful for classifying the received signals in the
embodiment of FIGURE 2.
Referring first to FIGURE 1, an ultrasonic
diagnostic imaging system constructed in accordance
35   with the principles of the present invention is shown

in block diagram form. This system operates by
scanning a two or three dimensional region of the
body being imaged with ultrasonic transmit beams. As
each beam is transmitted along its steered path

5   through the body, the tissue and blood flow in the
body return echo signals with linear and nonlinear
(fundamental and harmonic) components corresponding
to the transmitted frequency components. The
transmit signals are modulated by the nonlinear

10   effects of the tissue through which the beam passes
or the nonlinear response of a contrast agent
microbubble encountered by the beam, thereby
generating echo signals with nonlinear components.

        The ultrasound system of FIGURE 1 utilizes a
15   transmitter 16 which transmits waves or pulses of a
selected modulation characteristic in a desired beam
direction for the return of harmonic echo components
from scatterers within the body. The transmitter is
responsive to a number of control parameters which

20   determine the characteristics of the transmit beams
as shown in the drawing, including the frequency
components of the transmit beam, their relative
intensities or amplitudes, and the phase or polarity
of the transmit signals. The transmitter is coupled

25   by a transmit/receive switch 14 to the elements of an
array transducer 12 of a probe 10. The array
transducer can be a one dimensional array for planar
(two dimensional) imaging or a two dimensional array
for two dimensional or volumetric (three dimensional)

30   imaging.

        The transducer array 12 receives echoes from the
body containing fundamental and harmonic (nonlinear)
frequency components which are within the transducer
passband. These echo signals are coupled by the

35   switch 14 to a beamformer 18 which appropriately

delays echo signals from the different transducer
elements, then combines them to form a sequence of
fundamental and harmonic signals along the beam from
shallow to deeper depths. Preferably the beamformer
5   is a digital beamformer operating on digitized echo
signals to produce a sequence of discrete coherent
digital echo signals from a near field to a far field
depth of field. The beamformer may be a multiline
beamformer which produces two or more sequences of
10   echo signals along multiple spatially distinct
receive scanlines in response to a single transmit
beam, which is particularly useful for 3D imaging.
The beamformed echo signals are coupled to an
ensemble memory 20.
15   In accordance with one aspect of the present
invention, multiple waves or pulses are transmitted
in each beam direction using different modulation
techniques, resulting in the reception of multiple
echoes for each scanned point in the image field.
20   The echoes corresponding to a common spatial location
are referred to herein as an ensemble of echoes, and
are stored in the ensemble memory 20, from which they
can be retrieved and processed together. The echoes
of an ensemble are processed in various ways as
25   described more fully below to produce the desired
fundamental or harmonic signals. The echo signals
are processed by a B mode signal path including a
grayscale signal processor 22 and by a Doppler signal
path including a Doppler processor 24. In the
30   illustrated embodiment the Doppler processor is
provided in an ASIC (application specific integrated
circuit) which includes two parallel paths for the
processing of two Doppler signals at the same time.
These paths are shown as Doppler processor A and
35   Doppler processor B in the drawing.

The grayscale and Doppler processors can be
operated individually in the conventional manner to
produce a grayscale image or a Doppler image, or a
colorflow image which is formed by the overlay of a
5   fundamental or harmonic grayscale tissue image with
Doppler flow information. In accordance with the
present invention signals from the grayscale and
Doppler processors 22 and 24 are coupled to a
classifier 30. In a constructed embodiment the
10   classifier is formed by software running on a CPU
which analyzes the received signals and decides
whether a received signal should be displayed as a
pixel in a flow image or a pixel in a perfusion image
or both. For example a large vessel may be
15   visualized in both a perfusion image and a flow
image. The signal is appropriately stored in an
image memory 32 which is partitioned into a flow
image section and a perfusion image section. The
flow and perfusion images are further processed as by
20   scan conversion and combined in an overlay of the
flow image overlaying the perfusion image by an image
processor 36. Alternatively the flow information can
be embedded in the perfusion image in the image
memory. Additionally the flow and perfusion images
25   can overlay an image of the tissue background. The
resultant image is displayed on an image display 38.
        The vascular flow and/or perfusion images may be
alternatively removed via a user control either in
review of a Cineloop sequence or during live imaging.
30   This enables the clinician to view the perfusion
image over tissue, the flow image over tissue or both
tissue and flow together over tissue. It also
enables either perfusion or flow to be viewed in
isolation from other information. The transparency
35   of the perfusion and flow images can be altered to

enable visualization of perfusion, flow and
background tissue images together. For example, when
the microcirculation is filled with microbubbles the
perfusion image may largely obscure underlying tissue

5   or flow. The perfusion may then be displayed in a
semi-transparent mode so that the clinician can view
the underlying tissue or flow while still
appreciating the tissue perfusion.
        In use, an ultrasonic contrast agent is

10   introduced into the patient's vascular system and
imaging of a region of interest such as the liver
commences at a low MI. Initially, before the
contrast agent arrives at the region of interest, a
tissue image is formed by signals received from

15   tissue. These signals are processed by a background
tissue signal processor in the B mode signal path.
The background tissue signal processor produces an
image of the background tissue in the region of
interest in a manner similar to the processing of the

20   grayscale signal processor 22, but with thresholds
set to detect signals from tissue. The tissue
signals may be fundamental or harmonic. Generally
fundamental signals are preferred when operating at a
low MI where tissue harmonic signals will be at low

25   levels. The background tissue image is coupled to
the image processor 36 where it is displayed
initially as just a tissue image, then as a
background to flow and perfusion as the contrast
agent begins to fill the region of interest.

30   The larger arterial vessels in the region of
interest will begin to light up first in the image as
the contrast agent will arrive in the larger vessels
first due to their higher flow velocities. The
larger vessels are displayed from the fundamental and

35   harmonic signals produced by flowing contrast agent

and detected by the Doppler processor 24. In time,
the contrast agent will begin to perfuse the tissue
surrounding the larger vessels and the microbubbles
slowly begin to perfuse the microvasculature of the
5   tissue. This filling of the microvasculature with
microbubbles increases the nonlinear signals detected
by the grayscale signal processor. This perfusion of
the tissue will then light up from the nonlinear
(harmonic) amplitude response of the signals produced
10   by the grayscale signal processor. The displayed
image will thus appear as a contrast perfusion image
containing larger vessels of more rapidly flowing
contrast microbubbles. The signal paths A and B of
the Doppler processor 24 are operated at the harmonic
15   and fundamental frequencies respectively. In a
constructed embodiment this fundamental and nonlinear
mixing enables the display of the larger vessels in
the near field as nonlinear (harmonic) contrast
segments and the larger vessels in the far field as
20   linear fundamental contrast segments, thereby
compensating for the attenuation of higher harmonic
frequencies from the deeper depths. The fundamental
and harmonic signals may be blended together into one
flow image, thereby showing larger vessel flow over a
25   considerable depth of field against a background of
perfused tissue.

     A variety of different transmit sequences may be
employed to detect the nonlinear signal components.
Harmonic separation is preferably performed by what
30   is known as "pulse inversion," by which the echoes
from multiple, differently modulated transmit pulses
are combined to separate the harmonic components and
attenuate linear fundamental components. The
different modulation may be different phase
35   modulation, polarity modulation, or amplitude

modulation, or a combination thereof as described in
US patent application serial number 60/527538, filed
December 5, 2003 and entitled "ULTRASONIC SPECKLE
REDUCTION USING NONLINEAR ECHO COMBINATIONS." For
5   example, a transmit sequence may comprise three
transmit pulses transmitted at the desired pulse
repetition interval (PRI) for the Doppler flow
velocities being detected, with the first pulse
having a nominal amplitude of 0.5 and a phase or
10   polarity of 0° or +, a second pulse having a nominal
amplitude of 1.0 and a phase or polarity of 180° or -,
and a third pulse having a nominal amplitude of 0.5
and a phase or polarity of 0° or +. When the echoes
from the three transmit pulses are normalized in
15   amplitude and additively combined the linear
fundamental frequency components cancel and the
harmonic components are enhanced. With amplitude and
phase modulation (see US Pat. 6,095,980 (Burns et
al.) and US Pat. 6,319,203 (Averkiou)) it is possible
20   to combine the nonlinear echoes in a way that some
energy at the fundamental frequency is present. This
energy is referred to herein as "nonlinear
fundamental" energy and it is the result of the
harmonic activity at unequal amplitudes. The
25   "nonlinear fundamental" should not be confused with
the linear response of a system with a single
excitation at the fundamental frequency. The
nonlinear fundamental can be used in both the
detection of perfusion and/or the detection of
30   vascular flow. Alternatively, pairs of differently
modulated pulses transmitted at a rapid rate to
prevent motion artifacts can be transmitted at the
PRI from one pulse pair to the next as described in
US patent 6,620,103 (Bruce et al.), which shows how
35   the pulse pairs can be spatially interleaved over

different transmit lines for low velocity flow
detection.

A detailed diagram of the grayscale and Doppler
processors is shown in FIGURE 2. The echo signals

5   from an ensemble of transmit pulses 1-N are applied
to the inputs of the processors. The grayscale
signal path 22 includes a quadrature bandpass filter
(QBP)42, which passes harmonic echo signals in a band
around $2f_o$. Construction and operation of a

10 quadrature bandpass filter is described in US Pat.
6,050,942 (Rust et al.) which explains how the filter
produces the I and Q components of an echo signal in
a desired passband. These components of an echo
ensemble are further filtered by the lowpass

15 characteristic of a matrix wall filter, which passes
echoes returned from tissue and stationary
microbubbles. The matrix wall filter may exhibit a
response characteristic such as that illustrated in
FIGURE 3a. The low pass filter response is seen to

20 roll off at PRF/2, half the repetition frequency of
the echo ensemble. For the case of pulse inversion,
fundamental frequency echo signals from tissue or
stationary microbubbles are contained in a band 62
located at the end of the passband, since the QBP is

25 operating in the harmonic band. Harmonic signal
components are located in a band 64 at the nominal DC
point of the filter response. The filtered ensemble
of echoes is applied to an estimator 52 which
combines the echo signals to separate the nonlinear

30 second harmonic signal components and detects the
signal power or amplitude squared. This signal path
functions in the manner of a nonlinear pulse
inversion processor to pass nonlinear signals from
stationary or nearly stationary microbubbles which

35 have perfused tissue in the region of interest.

The second signal path 24A in this embodiment is
a Doppler processing path which includes a QBP 42b
set to pass harmonic frequencies. This could be the
same QBP as used in the grayscale signal path or

5   could be a separate QBP as shown in the drawing. The
signals passed by QBP 42b are filtered by a bandpass
matrix wall filter 46. This filter is designed to
detect harmonic flow signals as there is considerable
overlap of fundamental and harmonic components

10   produced by the QBP when broadband transmit pulses
are used. Nonlinear pulsing schemes other than phase
or polarity modulated pulse inversion (e.g.,
combinations of phase or polarity pulse inversion and
amplitude modulation) may be used in a similar

15   fashion to detect both perfusion and flow of contrast
agents and to separate linear and nonlinear
components even in the case of broadband transmit
signals. A response characteristic useful for this
first Doppler signal path is shown in FIGURE 3b. The

20   bandpass characteristic 70,70' is seen to have a stop
band at DC. The fundamental frequencies from
microbubbles are located as shown at 72, and at 74
for moving microbubbles, attenuated by the QBP 42b.
Harmonic signal components from stationary

25   microbubbles are located in a band 76 at the stop
band of the filter, and detectable signals from
moving microbubbles are located in the band 78. The
filtered harmonic flow signal ensemble is coupled to
an estimator 54 which estimates the harmonic flow

30   signals. These signals will exhibit good axial and
lateral resolution due to the high harmonic
frequencies and will exhibit good signal-to-clutter
ratios since the echoes from flowing microbubbles are
significantly stronger than returned tissue harmonic

35   signals. These echoes will thus provide good spatial

resolution by comparison with the blooming effect
which can be seen with fundamental frequency flow
detection.   Further details of harmonic Doppler
processing can be found in US Pat. 6,036,643 (Criton
et al.), which is in the context of tissue harmonic
Doppler.

     The third signal path 24B includes a QBP 42c set
to pass fundamental frequencies f_o.   The fundamental
frequency ensemble passed by this QBP is filtered by
a matrix wall filter 48 with a band pass
characteristic such as that shown in FIGURE 3c.
Harmonic components in the vicinity of the stop band
76 are attenuated, aided by the QBP response and
depth-dependent attenuation, as are echo signals from
stationary components in band 72 at the filter skirt.
Moving microbubbles will exhibit a relatively strong
response in band 74.   These echo signal components
will have a good signal-to-noise ratio in comparison
to harmonic signals, but will have a lower signal-to-
clutter response and exhibit relatively low spatial
resolution since strong fundamental frequency echo
signals are returned by both tissue and microbubbles.
Image segments using these echoes can exhibit some
blooming due to the high sensitivity of detection and
signal-to-noise ratio of the Doppler signal estimator
56.   Consequently, in a preferred embodiment, flow in
the near field utilizes the harmonic Doppler flow
signals produced by path 24A.   At deeper depths where
the harmonic frequencies become attenuated, the
fundamental Doppler flow signals are used for
display.   At intermediate depths the flow display is
a blend of the harmonic and fundamental signals,
making a varying ratio transition from 100% harmonic
to 100% fundamental over a transition depth region.
The blending of harmonic and fundamental signals with

depth is described in US Pat. 6,283,919 (Roundhill et
al.) Thus, flow can be shown in the perfusion and
flow image over a considerable depth of view.

The signals produced by the three processing
paths 22, 24A, and 24B are classified for use as
tissue, stationary microbubbles (perfusion) or
flowing microbubbles (in larger vessels) by the
classifier 30. This classification could be done on
the basis of the power and velocity estimates of the
wall filtered signals. In the illustrated embodiment
the classifier decides the image(s) in which to
display the echoes in response to a velocity variance
estimation path which includes a QBP 42d operating at
the fundamental frequency f_o, and a velocity variance
processor 50. As shown by the dashed line at the
output of the velocity variance processor, these
variance estimates may also be classified and used
for display. The variance estimate is computed as
the root mean square of the Doppler velocity
bandwidth, which, to a first order approximation, can
be estimated using an equation of the form $1-\dfrac{|R(1)|}{|R(o)|}$,

where R(o) is the echo value squared and can be
computed by

$R(o)=\dfrac{1}{N}\sum_{n=1}^{N}x(n)x^{*}(n)$ and R(1) is the magnitude of the

first lag of the autocorrelation of the echo values
and can be computed by

$R(1)=\dfrac{1}{N}\sum_{n=1}^{N}x(n)x^{*}(n-1)$. Using velocity for signal

segmentation is premised on the assumption that
tissue and microbubbles in microvasculature
(perfusion) move at relatively low velocities and
exhibit a relatively narrow dispersion of velocities,
and microbubbles in larger vessels move at relatively

higher velocities and exhibit a relatively wider
dispersion of velocities. A segmentation scheme such
as that shown in FIGURE 4a can be used by the
classifier 30 in response to calculations of mean

5   velocity. This scheme has two curves 82 and 84 which
divide the response into different regions. If, for
instance, a velocity estimate R(o) for a pixel
exhibits relatively low mean velocity (Doppler
frequency) <f> and relatively high power, it is

10   likely that the signal came from tissue and it will
be displayed in the perfusion image. These velocity
estimates will be in the region defined generally by
the area 86. Those signals exhibiting higher mean
velocities <f> and relatively lower power are likely

15   from flow, and signals classified generally in the
area 88 will be displayed in the Doppler flow image.
        Another classification scheme which is
predicated on variance estimates is shown in FIGURE
4b. Estimates R(o) with relatively narrow (low)

20   velocity variance and relatively significant power in
area 92 are likely lower velocity perfusion
microbubbles in the microvasculature of tissue and
will be displayed in the perfusion image. Estimates
R(o) which have somewhat less power but exhibit a

25   broader (higher) velocity variance in area 94 are
likely from flowing microbubbles and will be
displayed in the flow image. Signals below the
variance threshold 98 are classified as from tissue
with or without microbubbles in its microcirculation.

30   Signals below the amplitude or power threshold 96 are
classified as noise which exhibits broad, random
variance.
        Thus it is seen that both perfusion and blood
flow can be segmented and imaged simultaneously for

35   an extended period of time in a single displayed

image by imaging contrast at low MIs and utilizing
the concepts of the present invention.